REMARKS

Claims 39, 40 and 42 remain under active examination in the present application. Claim 39 has now been amended. Applicants respectfully assert that all amendments are supported by the original disclosure and do not introduce new matter. Moreover, Applicants further respectfully assert that the amendments merely clarify the scope of the claims.

Summary Of Record Of Interview

Applicant's attorney thanks Examiner Montanari for the telephonic interview which took place on October 10, 2007. Discussion of the claimed invention and the cited art helped crystallize the distinctions over the art and, we believe, define patentable subject matter. The amendments below summarizes the comments made by Applicant's attorney in that interview. By way of review, the elected claims are drawn to methods for treatment of airway hyper-responsiveness and/or airflow limitation associated with a respiratory disease involving an inflammatory response in a mammal, comprising administering to the lungs of a mammal a SP-C therapeutic agent.

During the telephone conversation, the 35 USC 112, first paragraph rejection for written description was discussed. Applicant suggested that the claims would be amended to delete language referring to the administration to "the surface of the airways and alveoli" of a subject and to put this in terms of delivery to the lungs by inhalation or aerosol, as described specifically in the specification. The Examiner expressed that this amendment would be considered and could potentially overcome the instant rejection. Applicants have now submitted such amendments.

Also discussed during the interview was the 35 USC 112, first paragraph rejection for enablement. Applicant expressed that the claims were enabled for a method for treating pulmonary disease in a subject as outlined in the specification. The Examiner expressed that he felt the specification did not provide enough guidance to enable a method for treating all pulmonary diseases in a subject. Applicants suggested limiting the methods to methods for treatment of airway hyperresponsiveness and/or airflow limitation associated with a respiratory disease involving an inflammatory response.

The Examiner expressed that this amendment would be considered and could potentially overcome the instant rejection and suggested that Applicants present additional experimentation regarding methods of treatment. Applicants have now submitted such amendments and additional data.

Therefore, in view of the breadth of the claims as amended and the guidance provided by the specification, one of ordinary skill in the art at the time of the invention would not have required an undue amount of experimentation to make and use the claimed invention. In light of this, it is submitted that the claims of the present application, as amended herein, are patentable and it is respectfully requested that the rejection under 35 U.S.C. 112, first paragraph be withdrawn.

Double Patenting

The Examiner has rejected claims 39, 40 and 42 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, and 8 of U.S. Patent No. 6,838,428 B2. Although the conflicting claims are not identical, the Examiner contends that they are not patentably distinct from each other because the instant claims are similar to said patented claims.

Applicants now submit a terminal disclaimer in compliance with 37 CFR 1.321(c) to overcome the provisional rejection based on a nonstatutory double patenting grounds present in the final claims.

Claim Rejections - 35 USC §112

The Examiner has rejected claims 39, 40 and 42 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new matter rejection.

Applicants have now amended the instant claim 39 to delete the previously added recitation that the claimed method of treating pulmonary disease in a subject comprises the administration to "the surface of the airways and alveoli" of a subject.

The Examiner also claims that the claimed method reads upon treating any pulmonary disease. Furthermore, the Examiner claims that, for example, lung cancer and asbestos lead to pulmonary disease and that the cancer and asbestos are chronic effectors of pulmonary disease. The Examiner states that "they would need to be treated/cured before the pulmonary disease would show any viable improvement in diagnosis." This is not a correct assertion. There is no need for an underlying disease to be cured, or even treated, in order for a subject to be treated and benefit from the methods of the present invention.

In the present methods, the term "treating" is intended to encompass curing as well as ameliorating at least one symptom of the condition or disease. It is not limited to the "exclusive" treatment and can be used in conjunction with treatments for underlying causes.

The Examiner claims that the claimed method is very broad in what is exactly being treated. The Examiner states that the "skilled artisan could not envision practicing the claimed method to treat all forms of pulmonary disease if other effecters (i.e. asbestos) exist."

However, in the present invention, it is not necessary to cure or even treat the underlying cause in order to use the current methods and gain the benefit of treatment in the lungs by the SP-C therapeutic.

In order to facilitate prosecution, Applicants have now amended the main claim 39 to read:

> A method of treating ~~pulmonary disease~~ airway hyperresponsiveness and/or airflow limitation associated with a respiratory disease involving an inflammatory response in a subject comprising the administration to the lungs ~~the surface of the airways and alveoli of~~ a subject administered by aerosol or inhalation in need of such treatment a therapeutically effective amount of a formulation comprising a SP-C therapeutic.

Applicants assert that such changes are clear from the specification. Delivery to the lungs is provided for in paragraphs 85 and 90. Delivery of a medicament to the lungs of a patient by inhalation or aerosol is shown in paragraphs 21, 82, 88, and 170. In addition, treatment of

pulmonary diseases comprising airway hyperresponsiveness and/or airflow limitation associated with a respiratory disease involving an inflammatory response is shown in paragraph 90.

In reviewing the present invention, surfactant protein C (SP-C), a 34-35 amino acid peptide expressed specifically in type II epithelial cells in the alveolus, is shown to influence surface properties of lung phospholipids to enhance surfactant functions. The present invention has been demonstrated by insights into various roles of SP-C provided by studies in patients with selective deficiency of SP-C gene or dominantly inherited mutations in the SP-C gene. For example, a dominantly inherited mutation in SP-C gene is assosciated with interstitial lung disease (ILD).

ILD includes a heterologous collection of uncommon disorders detected in individuals who present with progressive lung disorders associated with frequent pulmonary infections, exercise limitations, tachypnea and shortness of breath. In general, ILD is associated in alveolar inflammation, pulmonary infiltration with monocytes and macrophages, progressive loss of alveolar structure and pulmonary fibrosis.

The inventors have now demonstrated that genetic ablation of SP-C in mice causes a progressive severe pulmonary fibrosis, epithelial cell dysplasia in conducting airways, emphysema, alveolar vascular remodeling and right heart failure.

In one study, the authors evaluated bleomycin-induced lung fibrosis in mice with genetic deletion of *SFTPC*. Compared with wild-type (SFTPC+/+) controls, mice lacking surfactant protein C (SFTPC−/−) had greater lung neutrophil influx at 1 week after intratracheal bleomycin, greater weight loss during the first 2 weeks, and increased mortality. At 3 and 6 weeks after bleomycin, lungs from SFTPC−/− mice had increased fibroblast numbers, augmented collagen accumulation, and greater parenchymal distortion. Furthermore, resolution of fibrosis was delayed. Although remodeling was near complete in SFTPC+/+ mice by 6 weeks, SFTPC−/− mice did not return to baseline until 9 weeks after bleomycin. By terminal dUTP nick-end labeling staining, widespread cell injury was observed in SFTPC−/− and SFTPC+/+ mice 1 week after bleomycin; however, ongoing apoptosis of epithelial and interstitial cells occurred in lungs

of SFTPC−/− mice, but not SFTPC+/+ mice, 6 weeks after bleomycin. Thus, SP-C functions to limit lung inflammation, inhibit collagen accumulation, and restore normal lung structure after bleomycin.

Taken together with findings in humans bearing dominantly inherited gene mutations in SP-C support the concept that a deficiency of proSP-C or SP-C cause pulmonary diseases. These pathologies include idiopathic pulmonary fibrosis (IPF), desquamated interstitial pneumonitis (DIP) and other forms of ILD. Thus, administration of SP-C via aerosol or instillation by other pharmacological means represents a novel approach to the treatment of ILD. Likewise, SP-C gene replacement therapy provides new methods to treatment of these disorders. Furthermore, gene array analysis offers a diagnostic approach in populations of patients suspected of ILD.

Applicants have submitted the declarations of two distinguished researchers in the field (Glasser and Whitsett) as well as supporting literature by Hokuto and Ikegami to show the feasibility of the claimed method. Submitted herein, is a Supplemental Information Disclosure Statement containing a further eleven publications showing the link between SP-C protein and the treatment of pulmonary inflammation

Additionally, as can be seen by the data, SP-C (-/-) knockout mice provide a model for testing therapies for pulmonary disease. Genetic ablation of SP-C caused a progressive severe pulmonary fibrosis, expression of the mucin gene MUC5 in the conducting airways, epithelial cell dysplasia in conducting airways, emphysema, and alveolar vascular remodeling Surprisingly, severe lung pathology developed in the absence of associated abnormalities in surfactant concentrations, and minimal alterations in surface properties of pulmonary surfactant isolated from the lung of SP-C (-/-) mice. These findings demonstrate that a specific lack of SP-C/proSP-C *per se*, causes severe lung disease mimicking an inflammatory response.

The pathology of the lung disease includes idiopathic pulmonary fibrosis (IPF), desquamating interstitial pneumonitis (DIP), usual interstitial pneumonitis (UIP), non-specific interstitial pneumonitis (NSIP), and other forms of interstitial lung disease.

The present invention provides for the treatment intended to be local. Applicants have now amended the claims to clarify such local delivery by inhalation and/or aerosol delivery to the lungs.

In the previously submitted Declarations and supplemental Information Disclosure Statement, Applicants have submitted several references demonstrating the feasibility of this therapy with SP-D and SP-B for acute diseases as tested in mice or sheep (see, for example, Hokuto et al., J. Clin. Invest. 113:28-37, 2004; Ikegami et al., Am. J. Physiol. 288:L552-L561, 2005; and Ikegami et al., Am. J. Respir. Crit. Care Med. 173:1342-1347, 2006). Therapy with SP-B, SP-C, and SP-D has been highly effective in rodent and sheep models of acute lung disease, and there is no reason to expect that they cannot be delivered chronically by aerosol or instillation and used successfully as a treatment for pulmonary inflammatory diseases.

The references provided by the Applicants use both recombinant SP-C-like peptides, recombinant SP-D, and purified SP-B as examples for therapy of acute lung disorders. Patients with mutations in the SP-C gene generally do not produce the active peptide (SP-C) needed in the airway. Even when the mutation is heterozygous, processing of the normal preproprotein (proSP-C) to active SP-C is inhibited by the mutant protein. Thus, replacement of the SP-C peptide to the lung represents a potential therapy.

Applicants have shown that deficiency of SP-C *per se* also causes severe lung disease in the knockout mice and have identified human patients that lack expression of both proSP-C and SP-C; therefore replacement of SP-C represents a potential therapy for this rare subset of patients when given into the lung. Finally, clinical mutations in which proSP-C is misprocessed or its synthesis is inhibited secondarily, as in severe lung injury, will have a decreased SP-C that can be replaced by delivery of the recombinant protein to the lung. Applicants have also shown that in conditions in which a surfactant protein is deficient, but not absent, additional surfactant protein can prevent further lung injury (*e.g.* as shown in Hokuto et al., J. Clin. Invest. 113:28-37, 2004).

Applicants assert that similar preparations are utilized routinely for the surfactant therapy of acute respiratory distress syndrome in premature infants. These infants have been successfully treated for many years in clinical practice. References given are standard for delivery of protein to the lung, and are not intended for systemic delivery of the peptide. Surfactant therapy for acute lung disease (RDS) in preterm infants, providing a lipid or lipid-protein mixture to the lung has been a standard therapy for RDS in preterm infants for more than 25 years (see, for example Whitsett, J.A.: Pulmonary surfactant and respiratory distress syndrome in the newborn infant. In: The Lung: Scientific Foundations, 2nd Edition, R.G. Crystal, J.B. West, E.R. Weibel and P.J. Barnes (*eds.*). Raven Press, New York, NY, Chapter 165:2167-2177, 1996).

The present invention provides for methods for treatment of airway hyperresponsiveness and/or airflow limitation associated with a respiratory disease involving an inflammatory response in a mammal, comprising administering to the lungs of a mammal a SP-C therapeutic agent. The references submitted, taken together, show that the SP-C therapeutic acts to treat inflammatory disease of the lung.

In view of the submitted Declarations, cited references and the claim amendments, Applicants submit that a skilled artisan would have sufficient guidance in the instant disclosure to make and use the full scope of the claimed embodiment. One of normal skill in the art would be able to rely on the state of the art of *in vivo* protein therapy to practice the claimed method in view of the disclosure regarding a method of treatment in the instant specification.

Thus, Applicants respectfully request that the rejections based on 35 USC 112 be withdrawn.

CONCLUSION

In light of the amendments and remarks made herein, it is respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited. Applicants encourage

the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

JEFFREY A. WHITSETT, *et al.*

By _____

Stephen R. Albainy-Jenei
Registration No. 41,487
Attorney for Applicant(s)
FROST BROWN TODD LLC
2200 PNC Center
201 East Fifth Street
Cincinnati, Ohio 45202
(513) 651-6839
salbainyjenei@fbtlaw.com

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